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(54) Title: POLYMERIZABLE COMPOSITIONS AND METHODS OF USE

(57) Abstract: The present invention provides compositions comprising a first component and a second component, wherein the first component includes at least two polymerizable organic monomers, and wherein the second component includes an oligomer of a polymerizable organic monomer, a plasticizer and an opacificant agent, wherein said composition polymerizes upon contact with an anionic environment. The compositions are useful for filling, occluding, partially filling or partially occluding an unfilled volume or space in a mass in an anionic environment. The composition are also useful for ablating diseased or undesired tissue by cutting off the blood supply to the tissue.

POLYMERIZABLE COMPOSITIONS AND METHODS OF USE

FIELD OF THE INVENTION

The present invention relates generally to organic compositions and more specifically to polymerizable compositions and methods of use therefor.

BACKGROUND OF THE INVENTION

Research in organic polymer chemistry has led to the discovery of a variety of biocompatible polymeric materials. One important class of such materials is the cyanoacrylates. These materials have been used successfully in a variety of medical applications where traditional medical techniques or devices have been found wanting, such as for example, tissue adhesives, endovascular embolic agents, and the like. tissue adhesives have been in clinical endovascular use since the 1970's. Liquid acrylics are extremely useful as endovascular embolic agents because of their ability to create permanent vascular occlusion. Typical complications associated with the use of cyanoacrylates for embolization occur when there is occlusion of normal arterial branches or material penetration into critical venous outflow channels. Additionally, reflux of cyanoacrylate materials around the delivery catheter tip can result in permanent endovascular - catheter adhesion and attempts at withdrawal the catheter can produce catheter fracture, vascular damage with resultant dissection/occlusion, or avulsion of the involved vascular pedicle with resultant subarachnoid hemorrhage.

Alkyl α-cyanoacrylates are a homologous series of organic molecules which readily polymerize and can adhere to living tissues. The methyl homolog has been used in hemeostasis and non-suture wound closure since 1960.

Polymerization rate of alkyl α-cyanoacrylates is a function of alkyl chain length. It has been reported that alkyl α-cyanoacrylates with six or fewer carbon atoms in the alkyl chain polymerize rapidly upon contact with animal tissue.

Since the advent of *n*-butyl-2- cyanoacrylate, there has been little advancement in the science of cyanoacrylate embolization of vascular structures such as

arteriovenous malformations (AVM). Several properties of cyanoacrylates are advantageous for such embolizations, e.g. tissue adhesion, rapid polymerization when contacted with blood and tissue, and long-term biocompatibility. Rapid polymerization allows the liquid material to solidify in flowing blood inside arteries without passing through small channels into venous structures. However, this rapid endothermic polymerization may also release sufficient heat to damage surrounding tissue, for example, brain tissue.

Although catheter coatings have been developed to reduce the risk of inadvertent endovascular catheter fixation during embolization procedures. catheter - cyanoacrylate adhesion remains a problem during intravascular embolization. Also, the level of practitioner proficiency and the specific adhesive composition utilized play a major roles in these events.

Accordingly, there exists a continuing need for compositions that have the correct balance of polymerization rate, adhesiveness, biocompatibility, and radiopacity. The present invention describes such compositions.

SUMMARY OF THE INVENTION

In accordance with the present invention, there are provided compositions including a first component and a second component, wherein the first component includes at least two polymerizable organic monomers and wherein the second component includes an organic oligomer, a plasticizer, and an opacificant agent, wherein the total composition polymerizes upon contact with an anionic environment. The compositions of the present invention are useful for filling or partially filling and occluding, or partially occluding cavities or spaces in human or animal bodies. The invention compositions are also useful for ablating diseased or undesired tissue or organs by blocking the blood supply to the tissue or organs.

In another aspect of the present invention, there are provided methods for filling or partially filling and occluding or partially occluding cavities or spaces in a

human or animal bodies. Another aspect of the present invention provides methods for ablating diseased or undesired tissue or organs by blocking the blood supply to the tissue or organs. Other aspects of the present invention provide methods for treating arteriovenous malformations (AVM), methods for treating neural aneurysms, methods for treating uterine fibroids, methods for treating solid tumors, methods for treating uterine leiomyoma, and methods for sterilizing female mammals.

In a still further aspect of the invention, there are provided methods for the controlled delivery and fixation of therapeutic compositions, chemotherapeutic compositions, radiation devices, magnetic particles, or other agents to desired location in human or animal bodies.

In yet another aspect of the invention, there are provided methods for adhering a first section of mammalian tissue to either a second section of mammalian tissue or a non-tissue surface.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compositions including a first component and a second component, wherein the first component includes at least two polymerizable organic monomers and wherein the second component includes an organic oligomer, a plasticizer, and an opacificant agent, wherein the total composition polymerizes upon contact with an anionic environment.

The composition is useful for filling, occluding, partially filling or partially occluding an unfilled volume or space in a mass ("a space"). In particular, the composition is useful for filling an existing space, e.g., the lumen of a blood vessel, or the sac of an aneurysm, a space created by a transiently placed external device, e.g., a catheter or like device, a space created by a procedure, e.g., an excision or like procedure or implantation of an object, e.g., a stent or like device, or a space created by the composition; the composition is also useful for adhering tissue to tissue, or adhering tissue to a device. The composition has the property of polymerizing when it

comes in contact with an anionic environment, or when it is deployed *in situ* in an existing space, e.g., the lumen of a blood vessel, or the sac of an aneurysm, a space created by a transiently placed external device, e.g., a catheter or like device, a space created by a procedure, e.g., an excision or like procedure or implantation of an object, e.g., a stent or like device, or a space created by the composition.

In a preferred embodiment, the composition includes alkyl cyanoacrylates. In a particularly preferred embodiment, the first component of the composition includes, *n*-hexyl cyanoacrylate and methyl cyanoacrylate or 2-hexyl cyanoacrylate and methyl cyanoacrylate.

In another preferred embodiment, the second component includes an oligomer or polymer formed from a composition of alkyl cyanoacrylate monomer, an alkyl esterified fatty acid and an opacificant agent.

In yet another embodiment, the second component of the composition includes a halogenated oil. Preferred are iodinated and brominated oils.

In a still further preferred embodiment, the first component is comprised of two alkyl cyanoacrylate monomers, and at least one inhibitor. A particularly preferred embodiment of the first component includes n-hexyl cyanoacrylate, methyl cyanoacrylate and one inhibitor.

A particularly preferred composition includes a first component and a second component, wherein the first component includes methyl cyanoacrylate, *n*-hexyl cyanoacrylate, hydroquinone, *p*-methoxyphenol, and acetic acid, and wherein the second component includes an oligomer or polymer formed from *n*-hexyl cyanoacrylate monomer, an alkyl esterified fatty acid and an opacificant agent. In a most preferred embodiment, the alkyl esterified fatty acid is ethyl myristate and the opacificant agent is gold.

It is known to those of ordinary skill in the art that the predictability of polymerization properties of alkyl cyanoacrylate monomers is related to the purity of

the monomers that are used. These polymerization properties include but are not limited to, rate of polymerization and stability of the monomer during storage. Another advantage of substantially pure alkyl cyanoacrylates is that compositions incorporating substantially pure alkyl cyanoacrylates require smaller amounts of additives, e.g., inhibitors, stabilizers and the like, to obtain a desired result that would otherwise have require greater amounts of the same additive.

Another embodiment of the present invention provides a method for filling, occluding, partially filling or partially occluding an unfilled volume or space in a mass by administering a composition of the present invention with an administering means, including a means for stabilizing fluid flow distal or proximal to the body space being treated, and a means for delivering the composition to the desired body space. An embodiment of the administering means is where the means for stabilizing fluid flow distal or proximal to the body space being treated is in a first device, and the means for delivering the composition to the desired body space is in a second device. An embodiment of the first device includes a temporary inflatable balloon, or like structure, that is inflated to stabilize fluid flow distal or proximal to the body space to be treated, and deflated for removal after some period after the composition has been delivered. Optionally the balloon structure may be juxtaposed adjacent to the body space where the composition is deposited, and inflated such that the balloon structure maintains the composition at the body space while the composition is polymerizing, and deflated for removal after some period after the composition has been delivered. An embodiment of the the second device includes a catheter, or like device for delivering and depositing the composition of the present invention at a desired location. Another embodiment of the administering means is where the means for stabilizing fluid flow distal or proximal to the body space being treated, and the means for delivering the composition to the desired body space are within a single device or apparatus.

The types of unfilled volumes or spaces within the scope of the present invention includes, but are not limited to the following instances.

For example, one aspect of the present invention is a method of filling, occluding, partially filling or partially occluding an existing space, such as, a lumen of a passageway in the body, e.g., a blood vessel, a duct, an aneurysm, or a fistula. Examples of the types treatments covered by this method of use, include but are not limited to the following. The present invention is useful as a method of treating arteriovenous malformations (AVM) where the blood vessel(s) that feed the AVM are occluded thereby cutting off the blood supply to the AVM. The present invention is useful as a method to ablate diseased or undesired tissue by cutting off the tissue's blood supply. In particular, the present invention is useful as a method of treating a tumor having a discrete blood supply, where the blood vessel(s) that feed the tumor are occluded thereby cutting off the blood supply to the tumor resulting in diminished growth or death of the tumor. The present invention is useful as a method of preventing or mitigating the development of an aneurysm by creating a partial occlusion at a location in the blood vessel selected to modify the fluid dynamics within the vessel to mitigate the formation or development of an aneurysm. The present invention is useful as a non-surgical method of treating symptomatic uterine leiomyomas by embolizing/occluding the uterine artery. This method has been reported using a non alkyl cyanoacrylate composition in *Journal of Vascular and Intervention Radiology*, 10:891-894, July-August 1999. The present invention is useful as a method of sterilizing a female mammal by occluding the fallopian tubes thereby preventing the passage of the eggs from the ovaries to the uterus. The use of an occluding agent to sterilize a female mammal is disclosed in U.S. Patent No. 5,989,580 "Method of Sterilizing Female Mammals", herein incorporated by reference. The methods disclosed in this patent can be advantageously applied using the compositions of the present invention, and are within the scope of the present invention. The present invention is useful for obliterating the left atrial appendage. The left atrial appendage is derived from the left wall of the primary atrium. It has been observed that patients with atrial fibrillation have a predilection for thrombus to form in the left atrial appendage. A review of this condition and the current status of treatment is disclosed in the article, "Left Atrial Appendage: structure, function, and

transition from a liquid state to a soft solid and completing as a firm solid. With these properties composition B is ideally suited for applications where the composition must quickly adhere and polymerize in the surrounding anionic environment. Particularly advantageous applications for composition B is treatment of various types of aneurysms.

Another advantageous application for composition B is the treatment of fistulas, particularly those where it is desirable to have the resultant aggregate structure form close to the point of deployment.

Still another advantageous use for composition B is for the maintenance of homeostasis during surgery, such as, during hepatectomy, renal surgery, and during gynecologic tumor surgery.

Further, composition B can be used to treat certain types of varicose veins, where composition B is injected into the portal vein.

The present invention is useful for filling, occluding, partially filling or partially occluding an unfilled volume or space in a mass ("a space"). In particular, the composition is useful for filling an existing space, e.g., the lumen of a blood vessel, or the sac of an aneurysm, a space created by a transiently placed external device, e.g., a catheter or like device, a space created by a procedure, e.g., an excision or like procedure or implantation of an object, e.g., a stent or like device, or a space created by the composition; the composition is also useful for adhering tissue to tissue, or adhering tissue to a device. The composition has the property of polymerizing when it comes in contact with an anionic environment, or when it is deployed *in situ* in an existing space, e.g., the lumen of a blood vessel, or the sac of an aneurysm, a space created by a transiently placed external device, e.g., a catheter or like device, a space created by a procedure, e.g., an excision or like procedure or implantation of an object, e.g., a stent or like device, or a space created by the composition.

The present invention is useful as an embolic agent that selectively creates an embolic blockage in the lumen of a blood vessel, duct, fistula or other like body passageways.

The present invention can be prepared and maintained as a first component and second component until needed or the components may be combined and stored. Storage conditions depend upon the stabilizers chosen.

The cohesive characteristics of the invention are such that when the composition in administered into an anionic fluid environment, such as blood, the composition forms a single aggregate structure. Additionally, the adhesive characteristics are such that the composition attaches to the lumen of vessel, duct, fistula or other like body passageways, but not to the degree where the device depositing the composition will become fixed to it before the practitioner can remove it.

The present invention is radiopaque. Although this characteristic is not necessary for its function as an embolic agent, radiopacity allows the embolic block to be observed with x-ray or other such imaging techniques.

The rate of heat released during polymerization of the present invention is low enough such that the heat does not adversely effect surrounding tissues that may be heat sensitive, such as brain tissue.

The present invention and its biodegradation products are sufficiently non-histotoxic and non-cytotoxic so that its presence is well tolerated in the body.

The composition of the present invention is useful for filling, occluding, partially filling or partially occluding an unfilled volume or space in a mass ("a space").

The present invention provides a method for filling, occluding, partially filling or partially occluding an unfilled volume or space in a mass. The types of unfilled

volumes or spaces within the scope of the present invention includes, but are not limited to the following instances.

For example, the present invention is used as a method of filling, occluding, partially filling or partially occluding an existing space, such as, a lumen of a passageway in the body, e.g., a blood vessel, a duct, an aneurysm, or a fistula. Examples of the types treatments covered by this method of use, include but are not limited to the following. The present invention is useful as a method of treating arteriovenous malformations (AVM) where the blood vessel(s) that feed the AVM are occluded thereby cutting off the blood supply to the AVM. The present invention is useful as a method to ablate diseased or undesired tissue by cutting off the tissue's blood supply. In particular, the present invention is useful as a method of treating a tumor having a discrete blood supply, where the blood vessel(s) that feed the tumor are occluded thereby cutting off the blood supply to the tumor resulting in diminished growth or death of the tumor. The present invention is useful as a method of preventing or mitigating the development of an aneurysm by creating a partial occlusion at a location in the blood vessel selected to modify the fluid dynamics within the vessel to mitigate the formation or development of an aneurysm. The present invention is useful as a non-surgical method of treating symptomatic uterine leiomyomas by embolizing/occluding the uterine artery. This method has been reported using a non alkyl cyanoacrylate composition in the *Journal of Vascular and Interventional Radiology,* 10:891-894, July-August 1999. The present invention is useful as a method of sterilizing a female mammal by occluding the fallopian tubes thereby preventing the passage of the eggs from the ovaries to the uterus. The use of an occluding agent to sterilize a female mammal is disclosed in U.S. Patent No. 5,989,580 "Method of Sterilizing Female Mammals," herein incorporated by reference. The methods disclosed in this patent can be advantageously applied using the compositions of the present invention, and are within the scope of the present invention.

The present invention is an embolic agent that provides a method for selectively creating and placing an embolic blockage which mechanically blocks, totally or partially, the lumen of a blood vessel, duct, fistula or other body passageway. In particular, the current invention is particularly useful in blocking, totally or partially, or diverting the flow of blood through the lumen.

The present invention can be advantageously used to block blood flow to certain tissues or areas. For example, the present invention can be used to treat arteriovenous malformation (AVM). An AVM is a collection of abnormal blood vessels which are neither arteries or veins. These vessels are packed closely together to form the nidus of the AVM. Blood flow into the AVM nidus is through thinned, enlarged, tortuous vessels and is rapidly shunted into draining veins because the nidus contains no arterioles or capillaries to provide high resistance. Clinical symptoms experienced because of AVMs are bleeding, re-direction of blood from nearby normal structures, or seizures. The primary clinical problem associated with cerebral AVM is the potential for lethal hemorrhage. The current standard of care for treating AVMs is surgical removal, high energy radiation or embolization with particular devices.

Further, the present invention can be used for treating cancer by diverting or blocking blood flow to tumors, the present invention is particularly useful for treating tumors in areas that are not easily accessible for surgical intervention, for example, brain tumors.

Other advantageous uses of the present invention are for aortopulmonary closure; treatment of artery pseudoaneursym; hepatic artery vascular occlusion and for temporary vascular occlusion during co-administration of cytotoxic drugs; treatment of other types of vessels, for example, the composition can be used for creating tubal occlusions, fallopian tube occlusions, vas deferens occlusions, and urinary occlusions.

The present invention provides a method of filling, occluding, partially filling or partially occluding a space created by a transiently placed external device, such as,

a catheter balloon. Examples of the types of treatments covered by this method of use include, but are not limited to the following. The present invention is useful as a method of treating an aneurysm by filling the space within the aneurysm with a composition of the present invention, where the composition polymerizes in the space within the aneurysm, thereby preventing the rupture of the aneurysm. This treatment can be practiced using an administering means, including a means for stabilizing fluid flow distal or proximal to the body space being treated, and a means for delivering the composition to the desired body space. An embodiment of the administering means is where the means for stabilizing fluid flow distal or proximal to the body space being treated is in a first device, and the means for delivering the composition to the desired body space is in a second device. An embodiment of the first device includes a temporary inflatable balloon, or like structure, that is inflated to stabilize fluid flow distal or proximal to the body space to be treated, and deflated for removal after some period after the composition has been delivered. Optionally the balloon structure may be juxtaposed adjacent to the body space where the composition is deposited, and inflated such that the balloon structure maintains the composition at the body space while the composition is polymerizing, and deflated for removal after some period after the composition has been delivered. An embodiment of the the second device includes a catheter, or like device for delivering and depositing the composition of the present invention at a desired location. Another embodiment of the administering means is where the means for stabilizing fluid flow distal or proximal to the body space being treated, and the means for delivering the composition to the desired body space are within a single device or apparatus. Such apparatuses include, but are not limited to, catheters, catheter coils, catheter wires, catheter balloons, or like devices. Many examples of such devices are known to those of ordinary skill in the art. For example, U.S. Patent No. 5,795,331 "Balloon Catheter For Occluding Aneurysms of Branched Vessels", incorporated herein by reference, discloses a device and methods for delivering compositions, such as those of the present invention. The device described combines an inflatable balloon with a catheter as a single apparatus, where the balloon is distal or proximal to the opening of the catheter. The present

invention has been practiced following the procedure and utilizing like devices described in **Neurosurgery**, Vol. 31, No. 3, September 1992, page 591 "Carotid-Cavernous Fistula Caused by a Ruptured Intra-cavernous Aneurysm: Endovascular Treatment by Electrothrombosis with Detailable Coils." The reference describes a procedure using a temporary inflatable balloon catheter, and a catheter for placement of a detachable platinum coil. A temporary balloon occlusion is performed proximally to a fistula, and then followed by the insertion of a platinum detachable coil into the fistula. The temporary balloon occlusion stabilizes the immediate environment near the fistula from the disturbed flow, increased flow, turbulence, or combination thereof created by normal unrestricted blood flow, while a thrombus forms around the platinum wire. In the present invention, a temporary balloon occlusion performs a similar function of stabilizing the immediate environment near the body space to be treated, for example, a fistula or aneurysm, from the disturbed flow, increased flow, turbulence, or combination thereof created by normal unrestricted blood flow. The temporary balloon, optionally, may also be used to temporarily form a seal at the opening of the body space, while the composition that had been deposited in the body space is polymerizing to its final form. After a period of time sufficient for the polymerization to be completed, the temporary balloon catheter is deflated and withdrawn.

The present invention also provides a method of filling, occluding, partially filling or partially occluding a space created or resulting from a procedure, such as with the excision of tissue, or insufflation. Examples of the types of treatments covered by this method of use include, but are not limited to the following. The present invention is useful as a method of treating oozing capillaries following an excision procedure.

The present invention further provides a method of filling, occluding, partially filling or partially occluding a space created by the placement or implantation of an object, such as, a medical device. Examples of the types of uses covered by this method of use include, but are not limited to the following. The present invention is

useful as a method of restoring the normal fluid dynamics at the peripheral edges of a vascular stent by filling the dead spaces between the stent and the lumen wall created by the implantation of the stent.

Still another advantageous use is the controlling and smoothing the blood flow around stents. A major complication from the balloon angioplasty and the use of stents is disruption of the smooth flow of blood past and around the stent which can lead to the formation of blood clots and their associated complications. The composition of the present invention can be used to modify and make regular the slip streams of blood through and adjacent to the stent to mitigate or alleviate the cause of the turbulence, and such turbulence causing states.

The present invention further provides a method of filling, occluding, partially filling or partially occluding a space created by the composition itself, such as, where the composition is used as a bulking agent. Examples of the types of uses covered by this method of use include, but are not limited to the following. For example, a method of recreating normal external contours, such as following physical trauma.

The monomer component and second component of the present invention are combined just prior to use. The composition of the present invention is administered using any type of deployment device. The term "deployment device" refers to a device used to deploy fluids or compositions similar to those of the present invention, such as, a needle, catheter devices, catheter balloon, stereotaxic placement devices, or the like. Methods for using these devices are readily known to one of ordinary skill in the art, and such devices are commercially available. Such devices and methods are readily known to those of ordinary skill in art. For example in U.S. Patent 5,925,683 "Liquid Embolic Agents", herein incorporated by reference, there is disclosed a method for introducing liquid embolic agents/solutions into the human body to form precipitated embolic occlusion masses, and also how this method is used for treating hepatic tumors using portal vein embolism. In U.S. Patent 5,702,361 "Method for Embolizing Blood Vessels", herein incorporated by reference, there is disclosed a

method of embolizing a vascular site in a patient's blood vessel including of introducing, via a catheter, at the vascular site to be emobolized a non-particulate agent or a plurality of such agents, and delivering, via a catheter, to the vascular site a polymer composition including a biocompatible polymer, a biocompatible solvent and contrast agent, wherein the delivery is conducted under conditions where the polymer precipitate forms in situ at the vascular site resulting in the embolizing of the blood vessel and where the non-particulate agent is encapsulated within the precipitate. An administrating means can be used to deliver the composition of the present invention to a desired location, the administering means including, a means for stabilizing fluid flow distal or proximal to the body space being treated, and a means for delivering the composition to the desired body space. An embodiment of the administering means is where the means for stabilizing fluid flow distal or proximal to the body space being treated is in a first device, and the means for delivering the composition to the desired body space is in a second device. An embodiment of the first device includes a temporary inflatable balloon, or like structure, that is inflated to stabilize fluid flow distal or proximal to the body space to be treated, and deflated for removal after some period after the composition has been delivered. Optionally the balloon structure may be juxtaposed adjacent to the body space where the composition is deposited, and inflated such that the balloon structure maintains the composition at the body space while the composition is polymerizing, and deflated for removal after some period after the composition has been delivered. An embodiment of the the second device includes a catheter, or like device for delivering and depositing the composition of the present invention at a desired location. Another embodiment of the administering means is where the means for stabilizing fluid flow distal or proximal to the body space being treated, and the means for delivering the composition to the desired body space are within a single device or apparatus. Such apparatuses include, but are not limited to, catheters, catheter coils, catheter wires, catheter balloons, or like devices. Many examples of such devices are known to those of ordinary skill in the art. For example, U.S. Patent No. 5,795,331 "Balloon Catheter For Occluding Aneurysms of Branched Vessels", incorporated herein by reference, discloses a device and methods

for delivering compositions, such as those of the present invention. The device described combines an inflatable balloon with a catheter as a single apparatus, where the balloon is distal to the opening of the catheter. The present invention has been practiced following the procedure and utilizing like devices described in **Neurosurgery**, Vol. 31, No. 3, September 1992, page 591 "Carotid-Cavernous Fistula Caused by a Ruptured Intra-cavernous Aneurysm: Endovascular Treatment by Electrothrombosis with Detailable Coils." The reference describes a procedure using a temporary inflatable balloon catheter, and a catheter for placement of a detachable platinum coil. A temporary balloon occlusion is performed proximally to a fistula, and then followed by the insertion of a platinum detachable coil into the fistula. The temporary balloon occlusion stabilizes the immediate environment near the fistula from the disturbed flow, increased flow, turbulence, or combination thereof created by normal unrestricted blood flow, while a thrombus forms around the platinum wire. In the present invention, a temporary balloon occlusion performs a similar function of stabilizing the immediate environment near the body space to be treated, for example, a fistula or aneurysm, from the disturbed flow, increased flow, turbulence, or combination thereof created by normal unrestricted blood flow. The temporary balloon, optionally, may also be used to temporarily form a seal at the opening of the body space, while the composition that had been deposited in the body space is polymerizing to its final form. After a period of time sufficient for the polymerization to be completed, the temporary balloon catheter is deflated and withdrawn.

The composition of the present invention are administered with any type of commercially available needle, catheter devices, or stereotaxic placement devices, preferably in conjunction with imaging technology that provides the practitioner with guidance as to the placement of the composition. The compositions of the present invention can be used advantageously in conjunction with any embolization method that employs an embolizing agent, occluding agent, or such composition that creates an embolic block, or occlusion, or otherwise in effect is used for filling, occluding, partially filling or partially occluding an unfilled volume or space in a mass ("a space"). Delivery can also be made with a micro catheter made from or coated with

an agent that lessens the likelihood of accidental gluing of the device to the vessel, for example, hydrophilic coating and silicone derivative coatings.

The following examples are given to enable those of ordinary skill in the art to more clearly understand and to practice the present invention. The examples should not be considered as limiting the scope of the invention, but merely as illustrative and representative thereof.

EXAMPLE 1

Formulation of a typical first component

Material	Weight (G)	Moles
2-hexyl cyanoacrylate	1250	6.8964
hydroquinone	0.0764	0.000694
p-methoxyphenol	0.0874	0.000704
phosphoric acid	0.1693	0.001726

EXAMPLE 2

Preparation of a typical second component

To a Waring blender was added 0.50 G of sodium bicarbonate and 250 mL water. 18 mL was added dropwise into the center of blender while the blender was stirring on the high setting. After the addition of was completed, the mixture was stirred for another minute. The resulting solid oligomer was isolated via filtration, washed with 2 portions of water followed by one portion of methanol and dried *in vacuo*. 2.0 G of the this oligo (2-hexyl cyanoacrylate) was combined with 100 g of powdered gold and placed was placed into a standard laboratory blender and blended for one minute. The blender was agitated constantly during the blending to ensure that the gold did not settle during the blending. 1.020 g portions of the blended material were placed into previously cleaned vessels and to each vessel was added 500 mg of ethyl myristate of 99.8% purity.

Example 3

Comparison of catheter adhesion force for 2-hexyl cyanoacrylate and *n*-butyl cyanoacrylate compositions

This example demonstrates differences in adhesion to a catheter of an alkyl cyanoacrylate of the present invention and an n-butyl cyanoacrylate.

All the mixtures were injected through a TurboTracker™ micro- catheter device (Medi-tech/Boston Scientific, Watertown, MA). All mixtures were prepared immediately prior to use to prevent separation of the components or contamination. The catheter tips were placed at the bottom of 10 mm by 5 mm diameter wells filled with 0.2 mL of heparinized human whole blood. Through the micro-catheter, 0.15 mL of each embolic mixture was injected into each well, surrounding the tip of the micro catheter. Mixtures containing n-butyl cyanoacrylate were allowed to polymerize for 1.0 minute, and those containing 2-hexyl cyanoacrylate for 3.0 minutes. The micro-catheters were then extracted from the polymerized cyanoacrylates at a constant rate of 8.3 mm/sec (Model 1000 Materials Testing System; Instron, Canton, MA) and the forces required for extraction were measured and recorded. (Minibeam Force Transducer™, 25-lb capacity; Interface Advanced Force Measurement, Scottsdale, AZ). Five samples of each mixture were tested. Comparison of the results was performed using the student *t* test.

Table 1

Composition	Alkyl cyanoacrylate	opacificant	plasticizer	Adhesion Force (N)
1	2-hexyl	33% gold powder	20% ethyl myristate	0.41 ± 0.14
2	2-hexyl			1.00 ± 0.23
3	2-hexyl	33% Ethiodol™		0.28 ± 0.12
4	2-hexyl	50% Ethiodol™		< 0.05
6	n-butyl	33% Ethiodol™		1.83 ± 0.21
7	n-butyl	50% Ethiodol™		0.34 ± 0.14

Ethiodol™ = iodinated castor oil

The data presented in table 1 clearly demonstrate that 2-hexyl cyanoacrylate compositions have significantly lower adhesion to the catheter than do the corresponding n-butyl cyanoacrylate compositions.

EXAMPLE 4

Formulation of a monomer component with *n*-hexyl cyanoacrylate and methyl cyanoacrylate

A. A monomer component with *n*-hexyl cyanoacrylate is formulated with the following materials, *n*-hexyl cyanoacrylate, hydroquinone, *p*-methoxyphenol and glacial acetic acid. The hydroquinone and *p*-methoxyphenol are kept under reduced pressure in a desiccator over a drying agent. The glacial acetic acid is taken up in a syringe and the syringe and the inhibitor is weighed, an amount of glacial acetic acid is added, and the syringe with the glacial acetic acid is re-weigh to determine the

amount of glacial acetic acid that had been added. This process is repeated until the desired amount of glacial acetic acid is added.

The monomer component is analyzed by gas chromatography for purity under the following conditions.

Instrument Description: HP5890 Gas Chromatograph with HP chemstation software.

Column Description: Supelco Nukol (60 meters- length, I.D., 0.32 mm, Film Thickness 1μm)

Instrument Parameters: Method 1

Injector Temperature: 220°C

Detector Temperature: 280°C

Head Pressure: 15 PSI

Air Pressure: 35 PSI

Hydrogen Pressure: 40 PSI

Aux.: 60 PSI

Initial Oven Temperature: 140°C for 20 min.

Ramp: 5°C/min.

Final Oven Temperature: 200°C for 50 min.

A Splitless System:

Injection Volume: 1.0 microliter

The component is sufficient pure if the combined impurities present totals to less than 1%.

B. Following the procedures taught in Part A of the present Example, a monomer component with a combination of methyl cyanoacrylate and *n*-hexyl cyanoacrylate can be made.

In place of the amount of *n*-hexyl cyanoacrylate called for in the above procedure, a combination of methyl cyanoacrylate and *n*-hexyl cyanoacrylate is use. The amounts of each material used is determined according to the following ratio:

moles of methyl cyanoacrylate = 0.111 x moles *n*-hexyl cyanoacrylate

Example 5

Comparison of cyanoacrylate compositions

For conformal endovascular obliteration utility

Methods and Materials

Transparent silicone models of aneurysms representing both narrow and wide neck configurations were constructed. Model A consisted of a straight 4mm tube with three 7mm aneurysms attached. The neck diameter was 3mm. Model B consisted of a helical 4mm tubing containing four aneurysms positioned along the greater curvature. Two were 5mm in diameter (1 having a 2mm neck, and the other having a 4mm neck), and two were 9mm in diameter (1 having a 3mm neck, and the other a three by 5mm neck). The helical model ended in a bifurcation; a 4mm wide neck aneurysm was positioned at the bifurcation to simulate a basiler tip aneurysm.

Twelve compounded cyanoacrylates were tested, six based upon the 2-hexyl cyanoacrylate / methyl cyanoacrylate monomers, six based upon the 1-hexyl cyanoacrylate / methyl cyanoacrylate monomers. Additives consisted of various oils, gold for opacification, and polymerization retardants. The silicone aneurysms were

filled with heparinized pig blood, and were injected with microcatheters under direct visualization during static conditions, and under fluoroscopic guidance during pulsatile flow conditions.

Model A was filled with heparinized pig blood, and each of the twelve compounds was injected into three aneurysms, directly visualizing the degree of filing. The models were then radiographed, opened, and the contents examined by microscopy.

Model B was perfused with heparinized pig blood, pulsatile flow, 40 centimeters per second. The mixtures were introduced via micro-catheters; injection was controlled with fluoroscopic visualization.

All twelve compounds remained cohesive and conformed nicely to the outline of the aneurysm. Many of the mixtures based upon the 2-hexyl monomer exhibited delayed polymerization, and could not be kept within the aneurysm lumen, even with adjacent balloon control of the infusion process. Four of the mixtures based upon the 1-hexyl monomer gave good cohesion, good conformation, remained within the aneurysm, and allowed some degree of angioplasty and remodeling of the arterial lumen by silicone balloon

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity and understanding, it will be apparent to those of ordinary skill in the art in light of the teaching of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the claims.

WHAT IS CLAIMED IS:

1. A composition comprising a first component and a second component, wherein the first component includes at least two polymerizable organic monomers, and wherein the second component includes an oligomer of a polymerizable organic monomer, a plasticizer, and an opacificant agent, wherein the composition polymerizes upon contact with an anionic environment.

2. The composition according to claim 1, wherein at least one of said polymerizable organic monomers is an alkyl cyanoacrylate.

3. The composition according to claim 2, wherein both of said polymerizable organic monomers are alkyl cyanoacrylates.

4. The composition according to claim 2, wherein said alkyl cyanoacrylates are chosen such that the alkyl chain contains from 1 to 18 carbon atoms.

5. The composition according to claim 2, wherein said cyanoacrylates are selected from methyl cyanoacrylate,
n-butyl cyanoacrylate, isobutyl cyanoacrylate, n-hexyl cyanoacrylate, 2-hexyl cyanoacrylate, n-octyl cyanoacrylate, or 2-ethylhexyl cyanoacrylate.

6. The composition according to claim 1, wherein said first component includes at least one polymerization inhibitor.

7. The composition according to claim 6, wherein said inhibitors act primarily to inhibit free radical polymerization.

8. The composition according to claim 7, wherein said inhibitors are present in the range of about 1 to 500 parts per million.

9. The composition according to claim 6, wherein at least one of said inhibitors acts primarily to inhibit anionic polymerization.

10. The composition according to claim 9, wherein said inhibitor is an acid.

11. The composition according to claim 10, wherein said acid is present in the range of about 50 to 500 parts per million.

12. The composition according to claim 11, wherein said acid is acetic acid or phosphoric acid.

13. The composition according to claim 12, wherein said acetic acid or phosphoric acid is present in the range of about 200 to 300 parts per million.

14. The composition according to claim 1, wherein said plasticizer is an esterified fatty acid.

15. The composition according to claim 14, wherein said esterified fatty acids are chosen from the group consisting of laurates, palmitates, oleates, myristates. or stearates.

16. The composition according to claim 15, wherein said esterified fatty acid is ethyl myristate.

17. The composition according to claim 1, wherein said opacificant agent is a metal.

18. The composition according to claim 17, wherein said metal is selected from gold, platinum, palladium, tantalum, titanium, or mixtures and alloys thereof.

19. The composition according to claim 18, wherein said metal is gold.

20. The composition according to claim 19, wherein said gold is in fine powder form with individual particles no larger than about 7 microns in diameter.

21. The composition according to claim 20, wherein said gold is in fine powder form with individual particles no larger than about 5 microns in diameter.

22. The composition according to claim 21, wherein said gold is in fine powder form with individual particles no larger than about 2 microns in diameter.

23. The composition according to claim 22, wherein said gold is in fine powder form with individual particles no larger than about 1 micron in diameter.

24. A composition comprising a first component and a second component, said first component comprising n-hexyl cyanoacrylate, methyl cyanoacrylate and phosphoric acid, said second component comprising an oligomer of n-hexyl cyanoacrylate, ethyl myristate, and gold, wherein said composition polymerizes upon contact with an anionic environment.

30. The composition according to claim 24, wherein said second component further includes a halogenated oil.

31. The composition according to claim 25, wherein said halogenated oil is iodinated castor oil.

27. A method of filling, occluding, partially filling, or partially occluding an unfilled volume or space in an anionic environment, said method comprising administering a composition comprising a first component and a second component, wherein said first component includes at least two polymerizable organic monomers, and wherein said second component includes an oligomer of a polymerizable organic monomers, plasticizer, and an opacificant agent, wherein said composition polymerizes upon contact with said anionic environment when administered with a device comprising a means for stabilizing fluid flow distal or proximal to said space and a means for delivering said composition to said space, whereby said space is filled, occluded, partially filled, or partially occluded.

28. The method according to claim 27, wherein said stabilizing means and delivering means are within one device.

29. The method according to claim 27, wherein said stabilizing means is in a first device, and said delivering means is in a second device.

30. The method according to claim 27, wherein said space is an existing space in human or animal body.

31. The method according to claim 30, wherein said existing space is created by a transiently placed external device.

32. The method according to claim 30, wherein said existing space is created by or resulting from a procedure.

33. The method according to claim 30, wherein said existing space is created by the placement or implantation of an object.

34. The method according to claim 30, wherein said existing space is created by the composition itself.

35. The method according to claim 30, wherein said existing space is a lumen of a passageway in the human body.

36. The method according to claim 30, wherein said existing space is a blood vessel.

37. The method according to claim 30, wherein said existing space is a duct.

38. A method for ablating diseased or undesired tissue, said method comprising administering a composition according to claim 1 to blood vessel(s) that feed said tissue, whereby said blood vessel(s) are occluded, thereby cutting off blood supply to said tissue, whereby said diseased or undesired tissue is ablated.

39. The method according to claim 38, wherein said undesired tissue is an arteriovenous malformation.

40. The method according to claim 38, wherein said undesired tissue is a tumor.

41. The method according to claim 38, wherein said undesired tissue is an uterine leiomyoma.

42. A method for treating arteriovenous venous malformation (AVM) by cutting off the blood supply to said AVM, said method comprising administering a composition according to claim 1 to blood vessel(s) that feed said AVM, whereby said blood vessel(s) are occluded, thereby cutting off blood supply to said AVM, whereby said AVM is treated.

43. A method for treating a tumor by cutting off the blood supply to said tumor, said method comprising administering a composition according to claim 1 to blood vessel(s) that feed said tumor, whereby said blood vessel(s) are occluded, thereby cutting off blood supply to said tumor, whereby said tumor is treated.

44. A method for treating a uterine leiomyoma by cutting off the blood supply to said leiomyoma, said method comprising administering a composition according to claim 1 to blood vessel(s) that feed said leiomyoma, whereby said blood vessel(s) are occluded, thereby cutting off blood supply to said leiomyoma, whereby said uterine leiomyoma is treated.

45. A method for sterilizing a female mammal, said method comprising administering a composition according to claim 1 to the fallopian tubes of said female mammal thereby preventing passage of eggs from the ovaries to the uterus of said female mammal, whereby said female mammal is sterilized.

46. A method of filling, occluding, partially filling, or partially occluding an unfilled volume or space in an anionic environment, said method comprising administering a composition comprising a first component and a second component, wherein said first component includes at least two polymerizable organic monomers, and wherein said second component includes an oligomer of a polymerizable organic monomer, a plasticizer, and an opacificant agent, wherein said composition polymerizes upon contact with said anionic environment when administered with a device comprising a temporary inflatable balloon and a catheter, whereby said space is filled, occluded, partially filled, or partially occluded.

47. A method for controlled delivery of a therapeutic, chemotherapeutic, or radiation delivery device, to a desired location in the human body, said method comprising combining said therapeutic, chemotherapeutic, or radiation delivery device with a composition according to claim 1, and delivering said combination to said desired location, whereby said therapeutic, chemotherapeutic, radiation delivery device, or gene therapy composition is gradually released at said desired location in the human body.

48. A method for delivering magnetic particles to a location in a mammalian body, said method comprising combining said magnetic particles with a composition according to claim 1, and delivering said combination to said location.

49. A method for adhering a first section of mammalian tissue to a second section of mammalian tissue, said method comprising contacting said first tissue with a composition according to claim 1, and contacting said second tissue with said first tissue, whereby said first tissue is adhered to said second tissue.

50. A method for adhering a section of mammalian tissue to a non-tissue surface, said method comprising contacting said tissue with a composition according to claim 1, and contacting said non-tissue surface with said section of mammalian tissue, whereby said tissue is adhered to said non-tissue surface.

51. The method according to claim 50, wherein said non-tissue surface is a medical device.

52. The method according to claim 51, wherein said medical device is a venous valve, a heart valve, or a stent.

53. A method for delivering a composition according to claim 1 to a location in a mammalian body, said method comprising administering said composition with a device comprising a means for stabilizing fluid flow distal or proximal to said location, and a means for delivering said composition, whereby said composition is delivered to said location.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/16638

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 31/05, 31/12, 31/275, 33/24
US CL : 424/9.4, 9.42, 78.31, 78.34, 78.35, 78.37, 422, 649, 667,723;514/772.3, 772.4, 772.6
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 424/9.4, 9.42, 78.31, 78.34, 78.35, 78.37, 422, 649, 667,723;514/772.3, 772.4, 772.6

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,713,235 B1 (KRALL) 15 December 1987 (15.12.1987), see entire document, expecially claims 1-15.	1-8, 27, 28, 30, 32, 35, 37, 38, 45, 49
X — Y	US 4,359,454 B1 (HOFFMAN) 16 November 1982 (16.11.1982), see entire document, especially column 2, lines 23-68, columns 3-8, claims 1-7.	1-18, 27-30, 35, 37, 45 — 19-23, 31-34, 36, 38-
Y	US 5,695,480 B1 (EVANS et al.) 09 December 1997 (09.12.1997), column 1, lines 65-68, column 2, lines 1-6, column 3, lines 60-68, column 4, lines 1-13, column 5, lines 63-	1-40, 42, 43, 45-53
Y	TSENG et al.. Modified ethoxyethyl cyanoacrylate for therapeutic embolization of arteriovenous malformation. J. Biomedical Materials Research. 1990, Vol. 24, pp. 65-77.	1-40, 42, 43, 45-53
Y	Database CAPLUS on STN, Acc. No. 1968:76778, (Columbus, OH USA) 68:76778 Woodward, S.C., Physiologoical biochemical evaluation implanted polymers. 1968, Vol.	1-40, 42, 43, 45-53
Y	US 5,981,621 B1 (CLARK et al.) 09 November 1999 (09.11.1999), column 6, lines 21-30, 34-51, column 18, claims 17,18.	1-40, 42, 43, 45-53
Y	SOVAK (Ed.). Radiocontrast Agents. 1984, pp. 348, 363.	1-40,42,43, 45-53
Y	EP 0 747 069 A2 (COOK INC.) 11 December 1996 (11.12.1996), column 3, lines 20-58, column 7, lines 56-58, column 8, lines 1-21, column 14, lines 19-39.	1-40, 42, 43, 45-68

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 July 2001 (26.07.2001)	19 SEP 2001
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer Frank Choi
Facsimile No. (703)305-3230	Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/16638

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,328,687 A (LEUNG et al.) 12 July 1994 (12.07.1994), column 3, lines 10-21, column 8, lines 21-68, column 9.	1-40, 42, 43, 45-53

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/16638

Continuation of B. FIELDS SEARCHED Item 3:
STN/CAS,WEST
Search terms: cyanoacrylate, ethiodized oil, hydroxyquinone, phosphoric acid, hydroxyphenol, ethyl myristate, gold, arteriovenous malformation